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Immunological Interaction between the Mother and Her Infant in Relation to the Development of Food Allergy

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Introduction

Infant immunity differs in many important respects from immune reactions in adults. The newborn baby is to a large extent immunologically naive and consequently many immune reactions represent primary responses. During the fetal period the immune system is suppressed and this is still the case at birth. Furthermore, the immunity of the newborn infant is influenced by maternal immunity, both transplacentally and via the breast milk. Thus, there is a close immunological interaction between the mother and her infant during the gestation and during the period of breast-feeding, by which the fetus receives protective factors and components that modify the immune system, as well as antigenic stimulation. The maternal health and immunity are therefore to be considered as important 'environmental factors' for the fetus and infant.

There is accumulating evidence that the conditions under which the primary encounter with ubiquitous food and inhalant allergens takes place may have a long, perhaps even life-long impact and to decide whether tolerance to the allergen will develop or whether sensitization and clinical manifestations of allergy are triggered. Recent evidence indicates that this encounter may occur already in fetal life.

Prenatal Interaction

The womb is the first environment that an individual encounters. Relatively little is known about the exchange of immunological information during the ges-

tational period between the mother and her offspring. The fetus is protected from various external influences by the placental barrier. This barrier is selective and, for example, maternal IgG antibodies and various antigens pass through it [1]. There is an active transport of IgG, as indicated by the higher levels in the cord blood than in the maternal serum. Their specificity depends on the maternal immunity. The barrier does in principle not allow the passage of other isotypes, nor of cells to the offspring. By increasing maternal intake of milk and egg, for example, during pregnancy, it is possible to increase maternal antibody concentrations to these foods and by increasing the intake there is a corresponding decrease in antibody concentration [2].

There are several ways by which transplacentally transferred immunity by maternal IgG antibodies may protect the baby. They reduce the risk for infections in the intestinal and respiratory tracts [3]. Such infections could possibly change mucosal barrier function and influence immune responses to antigens, including enhanced allergic sensitization.

There are also indications that maternal IgG antibodies against various foods may protect the infant from sensitization, although these studies were never published as full papers. Furthermore, in another, more recent and larger study this could not be confirmed [4].

In contrast to IgG, maternal IgE is supposed not to pass over the human placenta. The human fetus seems capable of producing IgE antibodies [5], but under normal circumstances this production is limited, as indicated by the low levels of IgE in cord blood. Elevated levels of cord blood IgE, i.e. above about 0.8 kU/l, do occur in some newborns and they are associated with an increased risk for the development of allergic disease during infancy and childhood [6]. The most likely explanation for the presence of elevated levels of IgE in cord serum of allergy-prone babies is a low-grade spontaneous synthesis of polyclonal IgE, alternatively by fetal IgE production against allergens passing through the placenta.

Transplacental transfer of maternal anti-idiotypic antibodies is a second possible explanation for the occasional finding in cord blood of IgE antibodies directed against various allergens [7, 8]. Such maternal IgG antibodies directed against the antigen-specific parts of other antibodies have a structure similar to the antigen and they can replace the antigen as an immunological stimulus. As a consequence, anti-idiotypic antibodies would have the capacity to stimulate fetal antibody formation against certain antigens. Such antibodies may also theoretically modulate infant immunity in other ways, either up- or down-regulating, depending on the circumstances.

Elevated levels of IgG anti-IgE antibodies in the cord blood appear to be associated with less allergy during the first 18 months of life [9]. This was particularly obvious in babies with a strong family history of allergy. This finding

would indicate that maternal immunity may be an important environmental factor influencing the risk for allergic manifestations in her child, even many years later. It is also possible that reports of a stronger influence of genetics, when atopy is inherited from the maternal side rather than from the paternal [10], are not explained by genetic imprinting but by an early environmental influence.

A third explanation is that fetal IgE production may possibly be a consequence of allergens passing through the placenta and inducing an immunological response in the fetus. This possibility is indicated by the observation that proteins, eaten by pregnant rats, can be isolated both in serum of their pups and in the amniotic fluid [11]. In humans, food allergens are often present in the serum of adults after ingestion of milk and egg, but so far there is no documentation of food allergens in the fetal circulation. There are occasional reports of low levels of IgE antibodies against cow's milk in some samples of cord blood [12–15]. Furthermore, positive skin prick tests have been elicited in newborns to penicillin, helminths, cow's milk and grass pollen [16–18]. In other, larger studies prenatal sensitization could not be confirmed [2, 19, 20]. It is reasonable to conclude that although the fetus is not completely protected from allergenic material, it is rarely sensitized in utero.

There are several recent reports indicating that the primary contact with allergens may take place during fetal life. Thus, T-cell responses to several inhalant and food allergens have been recorded in cord blood [21–24]. It is not known whether these immune responses are caused by exposure to the antigen or to anti-idiotypic antibodies.

It has been suggested that perinatal stress factors could represent environmental influences that would increase the risk for later appearing allergic disease [18]. These studies were retrospective, however, and did not control for various other possibilities. In unpublished studies we have not seen any indication for prematurity in itself as a risk factor for atopic sensitization.

Maternal Diet during Pregnancy

The fact that foods are the dominating allergens in infants, as well as the possibility of prenatal induction of IgE antibody formation, has prompted studies of maternal dietary restrictions during pregnancy as a means to prevent the development of the IgE antibodies and allergy in the babies. Some of these studies are however difficult to evaluate, as the maternal diet was not limited to pregnancy but continued into the lactation period [25].

Two prospective studies that were limited to studying the effects of dietary manipulation during pregnancy both failed to reveal any protective effect. In one of the studies, pregnant women with a family history of allergy were randomly

assigned to an unrestricted diet, or to an elimination diet during the last trimester of pregnancy [4, 26]. Allergenic foods like cow's milk, egg and fish were excluded in the intervention group. In another prospective study of similarly selected mothers, the participants either had a diet low in these foods, or had a diet with increased amounts of milk and eggs, i.e. at least 1 litre of milk and one egg daily [2, 27]. In contrast to the effect of dietary manipulation of breast-feeding mothers (see below), none of the diets during pregnancy were associated with a reduced risk for food allergy, nor of other symptoms of atopic disease in their babies. Thus, neither the avoidance of certain allergenic foods, nor increased amounts of them in order to stimulate IgG antibody formation had any appreciable effects on clinical symptoms.

The studies indicate that dietary manipulation of the mothers during pregnancy is not associated with less allergy in their babies, unless continued into the lactation period. Consequently, no dietary restrictions should be imposed on pregnant women for allergy prevention purposes.

Other Prenatal Factors

It has been reported that smoking, as compared to nonsmoking mothers, more often give birth to infants with a high neonatal IgE concentration [28]. These studies were however not conclusive, as they can be criticized from a methodological point of view. In contrast to the role of exposure to tobacco smoke after birth, the role of this prenatal is still not conclusively proven.

There are also indications that medication to pregnant women may affect the rate of allergy in their children. Observations include a possible increase in neonatal IgE concentration in babies of mothers treated with the β -blocking agent metoprolol [29]. Intrauterine exposure to metoprolol tended to be associated with more atopic disease during the first years of life, as compared to children of placebo-treated mothers.

The influence of maternal disease during pregnancy on the rate of allergic disease in their children has not been adequately assessed in prospective studies. There are however suggestions that the well-being of pregnant asthmatics may add to the genetic risk for development of atopic disease in their babies [18, 30].

In conclusion, although much remains to be studied, it is reasonable to assume that maternal immunity, health and medication, particularly during the final part of pregnancy all may have consequences for the incidence of allergy in their babies, at least during early childhood. Whether prenatal factors may also affect the change of allergy later in life remains to be studied.

Human Milk

Human milk contains numerous components that protect the infant against infections [31, 32]. They include factors that provide specific immunity, e.g. secretory IgA, low levels of IgG, IgM and IgE and viable lymphocytes. Of even larger importance is probably the presence of numerous factors, however, that provide nonspecific protection against potential pathogens, including gut colonization with nonpathogenic bacteria, lectins and other carbohydrates and lipids with antimicrobial, antiviral and antiprotozoan activity. Growth factors, including factors enhancing gut closure, are also present in the milk. Such factors are possibly of clinical significance, for example by reducing antigen uptake through the gut wall and by this reducing the risk for sensitization and the development of intestinal allergy.

There are also indications that human milk contains components that enhance the maturation of the immune system of the newborn infant. Several recent studies indicate that human milk may exert a regulatory role on infant immunity. Observations include an early stimulation of IgA antibody synthesis in breast-fed infants [33–35] and transfer of cell-mediated immunity [36, 37] and cytokines [37, 38]. Thus, human milk would not only provide passive protection against infections, but also actively stimulate infant immunity.

Human milk contains foreign antigens, e.g. food antigens eaten by the mother [31]. These may sensitize the baby [18, 20]. The small amounts of allergens that may be present in breast milk can, thus, be sufficient to cause a high grade of sensitization in a genetically predisposed infant and even to evoke allergic symptoms during lactation. These observations have prompted clinical studies in which the maternal diet was modified during pregnancy as a possible means to prevent sensitization and allergic manifestations in their babies. In some studies however, the maternal antigen avoidance diet was started already during pregnancy [25]. A reduced incidence of atopic dermatitis, urticaria and/or gastrointestinal disease was noted up to at least 12 months of age, but not later, and there was no effect on the incidence of asthma and rhinoconjunctivitis.

The effect of maternal hypoallergenic diet during the lactation period was addressed in a Swedish study [20, 39]. Mothers of infants with a family history of allergy either adhered to a diet with total avoidance of cow's milk, egg and fish products or had an unrestricted diet from the time of delivery and during the first 3 months of lactation. The infants were exclusively breast-fed for at least 3 months or, if this was not feasible, were given a hydrolysate formula. Both groups of infants were given a casein hydrolysate formula up to 6 months of age, if they were not fully breast-fed. The incidence of atopic dermatitis was significantly lower during the first 6 months of age in infants of mothers adhering to the hypoallergenic diet, as compared to the nondiet group. Furthermore, the

maternal diet restrictions resulted in a significantly lower rate of sensitization in the diet infants during the time of restrictions. The follow-up at 4 years of age showed a significant difference in the incidence of atopic dermatitis in the diet children compared with the nondiet children [39]. The incidence and prevalence of other atopic manifestations were similar in the two groups however.

In conclusion, the prospective studies in which the effect of avoidance of highly allergenic food by lactating mothers was evaluated indicate that such manipulation of the maternal diet in exclusively breast-fed infants may delay the onset of allergic sensitization and disease in their babies and also result in less severe disease in those that develop allergic symptoms. Thus, manipulation of the maternal diet may be worthwhile during the lactation period (but not during pregnancy) in families with a genetic predisposition for allergic disease. Maternal diet should, however, be employed only in selected cases and it should not be recommended indiscriminately, as it imposes a substantial emotional and social stress on the family as well as a risk for suboptimal nutrition of the mother. Furthermore, the families should be informed that the results of even a strict maternal hypoallergenic diet are at best modest.

Since sensitization occurs so often during breast-feeding, the thought itself suggests that high-risk infants should not be breast-fed at all but should rather be given hypoallergenic formula immediately after birth. However, in the light of all the other advantages of breast-feeding, including both biological and psychological advantages, such advice should not be given at present. Nevertheless, a careful evaluation of such a preventive measure is justifiable. Even though the results in the literature do not form the basis for any general preventive measures, they increase the insight into the process of sensitization and thereby help to increase our understanding of seemingly contradictory case histories that the parents sometimes give. The mother who, after weaning, reports that the child's eczema has got better, is probably just as right as the mother claiming that the eczema in her infant worsened when her child received an infant formula. In the first case, sensitization to eggs, for example, may have occurred and the amount of allergen in the breast milk was sufficient to provoke symptoms during lactation. An improvement then took place after weaning when the child was given ordinary food, which, for the children of that age usually contain no egg protein. Similarly, in the second case, sensitization to cow's milk, for instance, may have occurred, but not to such a degree that the small amounts of cow's milk transferred by breast milk provoked symptoms, while such symptoms were provoked when a cow's milk-based formula was introduced.

The precise relation between breast-feeding and infant allergy is thus not fully understood. It is reasonable to assume that any allergy-protective effects of breast-feeding may vary with the individual mothers, as both their diet and their immune status appear to play a role (table 1). Also, an allergy-preventing effect

Table 1. Breast-feeding and possible protection against allergic disease

Appears to delay the onset of allergy in genetically predisposed individuals
The allergy-preventive quality of milk may vary, e.g.:
Maternal diet
Maternal immunity
Several possible protective mechanisms, e.g.:
Protects against infections
Stimulates the maturation of the immune system
Low allergen content
Passive transfer of immunity

of human milk seems, however, to be limited to babies with a genetically determined increased risk for allergic disease [40]. This lends further support to the notion that environmental factors associated with an increased rate of allergic disease in children are mainly operative in individuals with a genetic propensity for allergic sensitization and disease.

Conclusion

There is a close immunological interaction between the mother and her baby which is operative throughout the gestation period and after birth until weaning. Thus, the mother does not only genetically influence her offspring but also represents a significant environmental factor early in life. Recent research has provided evidence that primary exposure to antigens may occur already during fetal life. The clinical significance of these observations are unknown.

Breast-feeding is of major significance to promote the health of the infant. This is particularly true in developing countries, but it has major advantages over formula-feeding also in wealthy, industrialized countries. Much more needs to be learnt about the complex immunological interplay between the mother and her baby through the breast milk.

References

- 1 Bramwell F: The transmission of antibodies; in Bramwell F (ed): *The Transmission of Immunity from the Mother to the Young*. Amsterdam, North-Holland, 1970, pp 242–250.
- 2 Lilja G, Dannaus A, Fälth-Magnusson K, et al: Immune response of the atopic woman and foetus: Effects of high- and low-dose food allergen intake during late pregnancy. *Clin Allergy* 1988;18:131–142.
- 3 Fallot M, Boyd J, Oski F: Breast-feeding reduces the incidence of hospital admissions for infection in infants. *Pediatrics* 1980;65:1121–1124.
- 4 Fälth-Magnusson K, Kjellman N-IM: Allergy prevention by maternal elimination diet during late pregnancy – A 5-year follow-up of a randomized study. *J Allergy Clin Immunol* 1992;89:709–713.
- 5 Miller DL, Hirvonen T, Gitlin D: Synthesis of IgE by human conceptus. *J Allergy Clin Immunol* 1973;52:182–188.
- 6 Kjellman N-IM: IgE determinations in neonates is not suitable for general screening. *Pediatr Allergy Immunol* 1994;5:1–4.
- 7 Hahn ZM, Carlsson B, Björkander J, Osterhaus AD, Mellander L, Hanson LÅ: Presence of non-maternal antibodies in newborns of mothers with antibody deficiencies. *Pediatr Res* 1992;32:150–154.
- 8 Mellander L, Carlsson B, Hansson L-Å: Secretory IgA and IgM antibodies to *E. coli* and poliovirus type 1 antigens occur in amniotic fluid, meconium and saliva from newborns. A neonatal immune response without antigenic exposure: A result of anti-idiotypic induction? *Clin Exp Immunol* 1986;63:555–561.
- 9 Vassella C, Odelram H, Kjellman N-I, Borres M, Vanto T, Björkstén B: High anti-IgE levels at birth are associated with a reduced allergy incidence in early childhood. *Clin Exp Allergy* 1994;24:771–777.
- 10 Cookson W, Young R, Sanford A, et al: Maternal inheritance of atopic IgE responsiveness on chromosome 11q. *Lancet* 1992;340:381–384.
- 11 Dahl GMK, Telemo E, Wessström BR, Jacobsson I, Lindberg T, Karlsson BW: The passage of orally fed protein from mother to foetus in the rat. *Comp Biochem Physiol* 1984;74:199–201.
- 12 Delespesse G, Sarfati M, Lang G, Schon A: Prenatal and neonatal synthesis of IgE. *Monogr Allergy*. Basel, Karger, 1983, vol 18, pp 83–95.
- 13 Businco L, Marchetti F, Pellegrini G, Perlini R: Predictive value of cord blood IgE levels in 'at risk' newborn babies and influence of type of feeding. *Clin Allergy* 1983;13:503–508.
- 14 Michel FB, Bousquet J, Greiller P, Robinet-Levy M, Coulomb Y: Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic disease in infancy. *J Allergy Clin Immunol* 1980;65:422–430.
- 15 Host A, Husby S, Gjesing B, Larsen J, Lowenstein H: Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. *Allergy* 1992;47:218–229.
- 16 Levin S, Altman Y, Sela M: Penicillin and dinitrophenyl antibodies in newborn and mothers detected with chemically modified bacteriophage. *Pediatr Res* 1971;5:87–88.
- 17 Weil G, Hussain R, Kumaraswami V, Tripathy S, Phillips K, Olesen E: Prenatal allergic sensitization to helminth antigen in offspring of parasite-infected mothers. *J Clin Invest* 1983;71:1124–1129.
- 18 Björkstén B, Gerrard J: Environmental and developmental factors in allergic disease in infancy and early childhood; in Marsh D, Blumenthal M (eds): *Genetic and Environmental Factors in Clinical Allergy*. Minneapolis, University of Minnesota Press, 1990, pp 84–96.
- 19 Croner S, Kjellman N-IM, Eriksson B, Roth A: IgE screening in 1,701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 1982;57:364–368.
- 20 Hattevig G, Kjellman B, Sigurs N, Grodzinsky E, Hed J, Björkstén B: The effect of maternal avoidance of eggs, cow's milk, and fish during lactation on the development of IgE, IgG, and IgA antibodies in infants. *J Allergy Clin Immunol* 1990;85:108–115.
- 21 Warner J, Miles E, Jones A, Quint D, Colwell B, Warner J: Is deficiency of interferon-gamma production by allergen-triggered cord blood cells a predictor of atopic eczema? *Clin Exp Allergy* 1994;24:423–430.

- 22 Rinas U, Horneff G, Wahn V: Interferon-gamma production by cord-blood mononuclear cells is reduced in newborns with a family history of atopic disease and is independent from cord blood IgE levels. *Pediatr Allergy Immunol* 1993;4:60-64.
- 23 Piccinni MP, Mecacci F, Sampognaro S, et al: Aeroallergen sensitization can occur during fetal life. *Int Arch Allergy Immunol* 1993;102:301-303.
- 24 Kondo N, Kobayashi Y, Shinoda S, et al: Cord blood lymphocyte responses to food antigens for the prediction of allergic disorders. *Arch Dis Child* 1992;67:1003-1007.
- 25 Zeiger R, Heller S, Mellon M, Helsey J, Hamburger R, Sampson H: Genetic and environmental factors affecting the development of atopy through age 4 in children of atopic parents: A prospective randomized study of food allergen avoidance. *Pediatr Allergy Immunol* 1992;3:110-127.
- 26 Fälth-Magnusson K, Öman H, Kjellman N-IM: Maternal abstention from cow's milk and egg in allergy-risk pregnancies. Effect on antibody production in the mother and the newborn. *Allergy* 1987;42:64-73.
- 27 Lilja G, Dannaeus A, Foucard T, Graff-Lonnevig V, Johansson S, Öman H: Effects of maternal diet during late pregnancy and lactation on the development of atopic diseases in infants up to eighteen months of age - In vivo results. *Clin Exp Allergy* 1989;19:473-479.
- 28 Halcken S, Host A, Nilsson L, Taudorf E: Passive smoking as a risk factor for development of obstructive respiratory disease and allergic sensitization. *Allergy* 1995;50:97-105.
- 29 Björkstén B, Finnström O, Wichman K: Intrauterine exposure to the beta-adrenergic receptor-blocking agent metoprolol and allergy. *Int Arch Allergy Appl Immunol* 1988;87:59-62.
- 30 Nelson H: Pregnancy and allergic diseases; in Bierman C, Pearlman D (eds): *Allergic Diseases of Infancy, Childhood and Adolescence*. Philadelphia, Saunders, 1980, pp 675-680.
- 31 Duchén K, Björkstén B: Sensitization via the breast milk; in Mestecky J (ed): *Immunology of Milk and the Neonate*. New York, Plenum Press, 1991, pp 427-436.
- 32 Goldman A: Immunologic system in human milk. *Pediatr Gastroenterol Nutr* 1986;5:343-345.
- 33 Avanzini MA, Plebani A, Monafò V, et al: A comparison of secretory antibodies in breast-fed and formula-fed infants over the first six months of life. *Acta Paediatr* 1992;81:296-301.
- 34 Pittard W, Bill K: Immunoregulation by breast milk cells. *Cell Immunol* 1979;42:437-441.
- 35 Prentice A: Breast-feeding increases concentrations of IgA in infants' urine. *Arch Dis Child* 1987;62:792-795.
- 36 Schlesinger J: Evidence for transmission of lymphocyte responses to tuberculin by breast-feeding. *Lancet* 1977;i:529-532.
- 37 Shiba T, Minagawa T, Mito K, et al: Effect of breast-feeding on responses of systemic interferon and virus-specific lymphocyte transformation in infants with respiratory syncytial virus infection. *J Med Virol* 1987;21:7-14.
- 38 Sarfati M, Vanderbeeken Y, Rubio-Trujillo M, Duncan DGD: Presence of IgE suppressor factors in human colostrum. *Eur J Immunol* 1986;16:1005-1008.
- 39 Sigurs N, Hattevig G, Kjellman B: Maternal avoidance of eggs, cow's milk, and fish during lactation: Effect on allergic manifestations, skin-prick tests, and specific IgE antibodies in children at age 4 years. *Pediatrics* 1992;89:735-739.
- 40 Björkstén B: Does breast-feeding prevent the development of allergy? *Immunol Today* 1983;4:215-217.

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